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## In This Issue



# Orlistat: A Brief Review

Obesity is a chronic condition that affects approximately one-third of the U.S. population. The prevalence of obesity has dramatically increased over the past two decades, and obesity has been identified as the second most common factor contributing to preventable death in the U.S. Obesity is a primary risk factor for the development of Type 2 diabetes, hyperlipidemia, hypertension, and other cardiovascular disorders. It also plays a role in the development of gallbladder disease, degenerative joint disease, respiratory disorders, and certain types of cancers. As a result, the economic burden of obesity is substantial. In 1995, the total economic cost of obesity-associated disease in the U.S. was estimated to be $99.2 billion.

### *Clinical Pharmacology*

Orlistat is a potent, specific, irreversible inhibitor of pancreatic and gastric lipases. Also known as tetrahydrolipstatin, orlistat is a chemically synthesized derivative of lipstatin, which is naturally produced by Streptomyces toxytricini. It exerts its pharmacologic activity by forming a covalent bond with the active serine site of gastric and pancreatic lipases in the lumen of the gastrointestinal tract. This action prevents these enzymes from hydrolyzing dietary fat (in the form of triglycerides) into absorbable free fatty acids and monoglycerols. Undigested triglycerides are eliminated through the fecal route. The lipase inhibition induced by orlistat decreases systemic absorption of dietary fat thereby resulting in a caloric deficit. Orlistat does not appear to inhibit the activity of other pancreatic enzymes, such as phospholipase $A_2$, amylase, or trypsin.

Data collected from pharmacokinetic studies using radiolabeled orlistat in both normal and obese individuals indicate that orlistat is not appreciably absorbed into the systemic circulation. Orlistat is excreted almost completely by the fecal route. Following an oral dose of 360 mg of $^{14}$C-orlistat in normal-weight and obese subjects, approximately 97 percent of the drug was recovered in the feces, with 83 percent as unchanged drug. Less than 2 percent was recovered in the urine, and complete excretion of total radioactivity occurred 3 to 5 days after dose administration.

### *Clinical Efficacy*

The results of two large, multicenter, double-blinded, randomized, placebo-controlled trials evaluating the efficacy of orlistat for the management of obesity for up to 2 years were recently published. Both studies, one conducted in the U.S. and the other in Europe, were similar in design. Davidson and colleagues compared orlistat to placebo for weight loss and weight maintenance in 892 obese patients (average weight = 100 kg, average BMI = 36 kg/m$^2$) who were otherwise healthy. All subjects were enrolled in a 4-week, single-blinded, placebo lead-in period during which they were instructed to consume an approximately 500 kilocalorie per day caloric deficit diet that provided 30 percent of total daily calories in the form of fat. Those patients who had a compliance rate of at least 70 percent (as judged by capsule counts) were stratified according to initial weight loss (< 2 kg and > 2 kg) and then randomized to receive either 120 mg of orlistat (n = 668) or placebo (n = 224) three times daily with meals for one year. The hypocaloric diet was continued throughout the first year of the study. At the end of one year, orlistat-treated patients who achieved 70 percent compliance were re-randomized to receive orlistat 60 mg, orlistat 120 mg, or placebo three times daily for an additional year. Placebo-treated patients continued to receive placebo. In an effort to stabilize body weight, the dietary intake of all subjects was

modified from a hypocaloric diet to a weight-maintenance diet for the second year of the study. All patients were required to attend dietary counseling and behavior modification sessions four times each year. The primary end point was change in body weight. Secondary end points included serum concentrations of total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, fasting glucose and insulin, as well as standing waist circumference and blood pressure. Fat-soluble vitamin serum concentrations and prothrombin time (to assess vitamin K status) were also evaluated.

During the 4-week placebo lead-in phase, patients lost approximately 2.3 kg and experienced an 8 percent decrease in total cholesterol and LDL. At the end of one year of treatment, 59 percent (133) of patients in the placebo group and 69 percent (458) of orlistat-treated patients remained in the study. Reasons for withdrawal were similar among the treatment groups. Orlistat-treated patients lost an average of 8.76 kg, which was statistically greater than the mean 5.81 kg loss of the placebo group ($p < 0.001$). In addition, 65.5 percent and 38.9 percent of orlistat-treated patients experienced > 5 percent and > 10 percent reductions in their baseline (prior to placebo lead-in phase) body weights, respectively, while only 43.6 percent and 24.8 percent of the placebo group achieved these degrees of weight loss.

By the end of two years of treatment, patients in both groups had regained some weight, but those who received the 120-mg dose of orlistat regained significantly less (35.2 percent regain) than those who received the 60-mg dose (51.3 percent regain) or placebo (63.4 percent regain). Thirty-four percent of patients treated with 120 mg of orlistat for two years maintained a weight loss of > 10 percent from baseline, as compared to 17 percent of patients in the placebo group ($p = 0.02$).

The total number of adverse events were similar between treatment groups. However, the orlistat group reported gastrointestinal events more frequently. For example, 79 percent of orlistat-treated patients, compared to 59 percent of those who received placebo, reported at least one gastrointestinal adverse event. In the orlistat group, common adverse events included flatus with discharge (40.1 percent), oily spotting (32.7 percent), fecal urgency (29.7 percent), fatty or oily stool (19.8 percent), oily evacuation (14.3 percent), fecal incontinence (11.8 percent), and increased defecation (11.1 percent). These events were reported to be of mild-to-moderate intensity and decreased during the second year of treatment. Vitamin supplementation was necessary for 14.1 percent of patients receiving 120 mg of orlistat and 6.5 percent of those receiving placebo in whom serum vitamin concentrations fell below the standard reference range.

Sjöström and associates evaluated the efficacy of orlistat in patients seen at obesity treatment centers throughout Europe. These investigators employed a study design similar to that used by Davidson. After completing a 4-week placebo lead-in phase and receiving instructions to follow a hypocaloric diet, 688 obese patients with an average BMI of 36 kg/m$^2$ (average weight = 99 kg) were randomized to receive either 120 mg of orlistat (n = 343) or placebo (n = 340) for one year. However, in this trial, patients from both treatment groups were re-randomized at the end of the first year either to continue the same regimen or receive the alternative treatment for an additional year. Diet was also modified for weight maintenance during the second year.

Weight loss after one year of treatment with orlistat in the European study was slightly greater than that observed in the U.S. study. Orlistat-treated patients lost an average of 10.3 kg compared to 6.1 kg in the placebo group ($p < 0.001$). Nine percent of orlistat-treated patients (compared to 2 percent in the placebo group) lost > 20 percent of their initial body weight, and 29.5 percent lost between 10 percent and 20 percent of their initial body weight (compared to 15.6 percent in the placebo group). At the end of the trial, 57 percent of the patients who received orlistat for two consecutive years maintained a weight loss of > 5 percent from baseline (prior to placebo lead-in). Weight regain in the orlistat-treated patients who were switched to placebo during the second year was significantly greater than for patients who continued treatment with orlistat (mean difference = 2.4 kg; $p < 0.001$). In general, adverse effects and vitamin replacement requirements were similar to those reported in the U.S. multicenter trial.

Results of these two clinical trials provide evidence that orlistat is more effective than placebo in promoting and then maintaining weight loss. However, several factors should be considered when using these data to formulate clinical decisions. Orlistat's effects on body weight may be different in general clinical practice. Patients enrolled in clinical trials were exposed to extensive and continuous dietary counseling and behavioral modification programs. Such resources are believed to have a substantial impact on overall weight loss, but may not be readily available or consistently applied in most clinical settings. Subjects in these trials were also selected for their adherence to the study medication during a 4-week lead-in period. Selection for adherence was again applied after one year of treatment, when subjects were re-randomized to orlistat or placebo. Thus, weight losses reported represent an ideal scenario, and actual weight loss might be predicted to be considerably smaller when orlistat is employed in the absence of organized behavioral modification programs and without subject selection. Total weight loss was generally reported from the beginning of the 4-week placebo lead-in period (prior to randomization). The best adherence to dietary restrictions, and thus the most rapid weight loss, generally occurs in the first month of therapy. Therefore, weight reductions that can truly be attributed to orlistat treatment alone may be smaller than that reported in these clinical studies. However, it should be noted that the change from a hypocaloric to a maintenance diet may have contributed to the weight regain during the second year of these studies.

Characteristics of patients who may be more likely to respond have not been identified. Although the authors of both studies reported that adverse effects were mild or moderate in severity, some patients may be unwilling

to tolerate the uncomfortable gastrointestinal adverse effects of orlistat that are more common and more severe early in treatment, before any substantial weight loss has been realized. In the U.S. study, the one-year drop out rate due to adverse effects in patients treated with orlistat was 9.1 percent compared to only 4.0 percent in the placebo group. The results of these trials may also be confounded by the possible unblinding of treatment groups due to the remarkable gastrointestinal effects experienced in the orlistat groups. It should be noted that during the U.S. multicenter trial, 4.9 percent of patients in the placebo group dropped out of the study during the first year due to "treatment failure," while only 0.9 percent of the orlistat-treated patients withdrew for this reason.

The long-term health benefits of orlistat are unclear. Health benefits accrued from the modest reductions in weight attributed to orlistat treatment are unkown. After two years of continuous orlistat treatment, patients lost an average of 4.5 percent of their initial body weight (approximately 4 kg). Although modest weight reductions (5 to 10 percent) have been reported to improve obesity-related risk factors, the effect of orlistat treatment on mortality remains to be determined.

### *Drug Interactions*

As many overweight or obese patients may be taking concomitant medications for obesity-related comorbidities, it is important to consider the potential for drug interactions with orlistat. Given that orlistat is minimally absorbed, the potential for clinically significant systemic drug interactions appears to be low. Several cross-over studies conducted in small numbers of normal healthy volunteers have shown that orlistat does not markedly affect the pharmacokinetics of oral contraceptives, warfarin, phenytoin, digoxin, glyburide, atenolol, furosemide, nifedipine, nifedipine extended-release tablets, captopril, or ethanol. However, orlistat did enhance the bioavailability and pharmacologic effect of pravastatin. The extent and clinical significance of this interaction remains to be determined, and the potential for drug interactions due to the pharmacological actions of orlistat within the gastrointestinal tract require further study. Although not well studied, the effect of dieting and dietary modification on the disposition of certain medications should also be considered.

### *Adverse Effects*

Safety data have been collected from more than 5,000 patients who were treated with orlistat during clinical trials. Major adverse effects of orlistat are gastrointestinal in nature, and are related to the pharmacological effect of orlistat as a lipase inhibitor. The most common gastrointestinal complaints include abdominal discomfort, liquid stools, soft stools, oily rectal spotting, flatulence and flatus with discharge, fecal urgency, fatty or oily stools, increased defecation, and fecal incontinence. At least one of these symptoms occurred in up to 95 percent of orlistat-treated patients during clinical trials. However, most symptoms were mild to moderate and did not persist for more than 4 weeks. Gastrointestinal adverse effects usually occurred within the first week of therapy and decreased with continued treatment.

Since orlistat is expected to decrease the amount of free fatty acids present in the gastrointestinal lumen by approximately 30 percent, theoretically it may impair gallbladder motility and predispose patients to stone formation. In one single-dose study in adults, orlistat did not affect gallbladder motility. However, the long-term effects on motility and possible sludge or gallstone formation is unknown. Safety concerns about the potential for the development of colon cancer, osteoporosis, renal oxalate stones, and vitamin deficiency associated with long-term orlistat-induced steatorrhoea have also been raised. Post-marketing studies are needed to evaluate the potential for these serious long-term adverse effects.

Orlistat inhibits pancreatic carboxylester lipase, the enzyme necessary for hydrolysis of vitamin esters and absorption of fat-soluble vitamins. During clinical trials, orlistat was shown to decrease fat-soluble vitamin absorption. The effect is most notable with vitamins D, E, and beta-carotene. Neither the absorption of vitamin A , nor the steady-state serum concentrations of retinol appear to be significantly affected after long-term treatment with orlistat. In addition, although vitamin $K_1$ concentrations were not monitored during clinical trials, there were no significant alterations in prothrombin time observed in orlistat-treated subjects. Orlistat does, however, significantly decrease the absorption of vitamin E and steady-state alpha-tocopherol plasma concentrations. During clinical trials alpha-tocopherol concentrations decreased in orlistat-treated patients. Plasma concentrations of alpha-tocopherol, however, did not often fall below the standard reference range, and low values were corrected with vitamin E supplementation. Vitamin D concentrations have been shown to decrease with long-term treatment of orlistat. After two years of orlistat therapy, subjects had an 8 percent decrease in 25-hydroxy-D concentrations. Calcium and parathyroid hormone concentrations were unchanged. As with vitamin E, 25-hydroxy-D concentrations remained within the normal reference range when vitamin D was supplemented. Orlistat also decreases the absorption of beta-carotene by approximately 30 percent. In clinical trials, the decrease in beta-carotene concentrations was also ameliorated by multivitamin supplementation.

### *Dosing and Administration*

Orlistat is FDA-approved for obesity management, for use during both weight loss and weight maintenance, in patients with an initial BMI > 30 $kg/m^2$ or for those with BMI > 27 $kg/m^2$ who also have other weight-related risk factors. When used for weight reduction, it should be prescribed in conjunction with a reduced-calorie diet. The lowest, maximum-effect dose of orlistat is 120 mg given three times daily, which inhibits approximately one-third of ingested dietary fat. Therefore, the recommended dose of orlistat is 120 mg administered three times daily during or up to 1 hour after each fat-containing meal. If a meal does not contain fat or if the patient skips a meal, the

orlistat dose may be omitted. Orlistat should be used in conjunction with a low-calorie diet containing less than 30 percent of calories from fat. Patients should be cautioned that consuming a high-fat diet along with orlistat may result in increased gastrointestinal adverse effects. Patients should also be instructed to take a standard multiple-vitamin supplement at least 2 hours before or 2 hours after orlistat administration. Because systemic absorption of orlistat is negligible, no dosage adjustments are necessary for patients with impaired end-organ function. Orlistat is not approved for use in children or adolescents under the age of 16 years, and no studies of the benefits or risks of orlistat in the pediatric population have been reported. Orlistat is available as 120-mg capsules, and the average wholesale price for ninety capsules is $118.80.

### *Summary and Conclusions*

Orlistat is the first antiobesity agent to be approved in the U.S. that exerts its full pharmacological effects in the gastrointestinal tract and does not primarily alter central nervous system neurotransmitters. By inhibiting gastric and pancreatic lipases in the lumen of the gastrointestinal tract, orlistat can prevent the absorption of nearly one-third of dietary fat. When combined with diet and behavior modification, orlistat produces significantly more weight loss than placebo, and induces modest improvements in the lipid profile, glucose control, and blood pressure. Orlistat therapy may also influence dietary choices because consumption of high-fat meals with the drug can lead to more severe gastrointestinal adverse effects. These adverse effects may be bothersome and intolerable for a small number of patients, but they tend to diminish with continued use of the medication. While orlistat appears to have a favorable safety profile, additional studies are needed to evaluate its long-term safety and potential for interactions with other medications. Available data suggest that, in selected patients, orlistat may prove to be an effective adjunct to diet and exercise for the management of obesity. Although orlistat's modest weight reduction may benefit obese patients, its efficacy for weight maintenance and effect on obesity-related morbidity and mortality remain to be determined. At present, orlistat should be used as monotherapy for obesity, as there have been no trials reporting the safety and efficacy of orlistat in combination with anorexiant medications.

***References available upon request.***

# Formulary Update

The Pharmacy and Therapeutics Committee recently approved the following formulary changes:

### *Additions*

- Rofecoxib (Vioxx®), a selective oral cyclooxygenase-2 inhibitor
- Oxcarbazepine (Trileptal®), an oral anticonvulsant
- Levetiracetam (Keppra®), an oral anticonvulsant
- Sterile talc for use in pleurodesis
- Polio virus vaccine (injectable)

### *Deletions*

- Polio virus vaccine (oral)
- Amphotericin B oral suspension (Fungizone®)

### *Editor's Note*

*We wish to thank Amy M. Heck, Pharm.D. and Jack A. Yanovski, M.D., Ph.D. for their contributions to this issue of* Pharmacy Update. *Please note that the clopidogrel and sirolimus review articles from the January/February 2000 issue were authored by Drs. Reem Abo-Zena and Barry Goldspiel, respectively.*




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